cyclase activity and intracellular cyclic-AMP generation. Here, we show that neurofibromin is required for normal murine lens development. Utilizing a previously developed strain of Nf1-deficient mice, we demonstrate that $Nf1^{-/-}$ embryos exhibit severe lens hypoplasia, and in some cases, anophthalmia. Currently we are working to elucidate the mechanistic molecular events responsible for this severe lens phenotype present in embryos devoid of systemic neurofibromin.

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Program/Abstract # 200
MAPK signaling during vasculature development in the mouse retina

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Neovascularization in the retina is associated with diseases that often cause severe vision loss and eventual blindness. In order to develop novel therapeutics, a better understanding of the molecular and cellular processes controlling vascular development in the eye is necessary. The mitogen-activated protein kinase (MAPK) pathway has been shown to play a pivotal role in vascularization in early embryonic development, as well as during tumorigenesis. Our laboratory has shown that MAPK inhibition reduces VEGF secretion, as well as angiogenesis and tumor growth, in melanoma and sarcoma xenograft model systems. However little is known about the role(s) of these signaling pathways in the development of the vasculature in the retina. To determine whether MAPK pathways are active during retinal vascularization in a mouse model, phosphorylated MAPK levels were analyzed. MAPK activation was undetectable at earliest stages of retinal vascularization but was elevated by PN7 through to PN21. In contrast, levels of total MAPK remained constant throughout this period. We observed that phosphorylated ERK became concentrated in the tips of budding vessels at PN7 and PN10. These observations indicate that MAPK pathways are active in regions that coincide spatially and temporally with extensive angiogenic remodeling of the developing retinal vasculature. This finding is consistent with our hypothesis that MAPK signaling is required for endothelial response to angioproliferative cytokines. These studies reveal the potential of inhibitors of MAPK signaling for application of treatment of neovascular retinopathies.

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Program/Abstract # 201
A role for TULP3 in mouse hedgehog signaling and neural patterning

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Neural patterning within the mammalian spinal cord and brain relies upon signaling cues from surrounding tissues, and the mouse neural tube serves as a good model to uncover genes involved in neural patterning. Through analysis of recessive mutations causing developmental and neural tube dorso-ventral patterning defects, our work identifies and characterizes novel Sonic hedgehog (Shh) signaling components based on changes in Shh-dependent cell identities. Mice mutant for Tubby-like Protein 3 (Tulp3) exhibit defects indicative of ectopic Shh signaling, such as exencephaly, polydactyly, impaired eye development, and overventralized patterning of the neural tube. Genetic epistasis analysis narrowed Tulp3's role within this pathway, and indicated that Tulp3's function depends upon cilia formation. Importantly, Tulp3 localizes to the primary cilium of mammalian cells where Shh pathway components such as Smoothened, Gli proteins, and Suppressor of Fused are also found. Although trafficking or processing events occurring in the cilium are not well understood, biochemical data from other organisms suggest that members of the Tubby family of proteins function in vesicular trafficking and/or signaling mediated through the cilium. Our work also demonstrates that Tulp3 interacts with CaMKII, a kinase involved in Ca^{2+}-dependent responses. Our current studies focus upon linking CaMKII to Shh signaling, and elucidating the mechanisms regulating Tulp3 subcellular localization.

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Program/Abstract # 202
Intraflagellar transport protein 122 is a novel antagonist of the murine Hedgehog signaling pathway

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Hedgehog signaling controls diverse developmental processes in metazoans. Recent studies indicate that the cilium acts as a sensory organelle for the mammalian Hedgehog signaling pathway. However, the mechanism by which the Hedgehog signals are transduced in mammals is not clearly understood. Through forward genetics we identified a null allele of mouse *Intraflagellar transport 122 homolog* (*mIft122*) that causes severe developmental defects. Genetic epistasis indicated that mIFT122 represses the Hedgehog pathway at a step downstream of Smoothened and upstream of Gli2. We found that mIFT122 plays a conserved role in the retrograde intraflagellar transport (IFT) in mammals, as the accumulation of IFT proteins at the distal tips of mutant cilia mimicked retrograde IFT defects in other species. Strikingly, activating components of the pathway, Gli2 and Gli3, accumulated to high levels at the distal tips of *mIft122* cilia, whereas the pathway repressor Suppressor of Fused did not. While previous studies have shown that the loss of IFT proteins involved in anterograde transport leads to the loss of cilia and *down-regulation* of the pathway, this study shows that loss of *mIft122*, predominately involved in retrograde transport, leads to strong, constitutive, and ligand-independent *up-regulation* of the pathway. Therefore, we propose that the bi-directional IFT machinery plays a more central role in Hedgehog signaling beyond construction of cilia and that the IFT machinery controls both the “on” and “off” states of the mammalian Hedgehog pathway at the tips of cilia.

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Program/Abstract # 203
Expression of EGF-responsive ERK5 in embryonic mouse submandibular glands

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Growth factors and their receptors regulate development of the submandibular gland (SMG) through activation of multiple intracellular signaling cascades including a mitogen-activated protein kinase